VERIFICATION OF TRANSLATION

I, Takayoshi Hirose residing at Takahashi Bldg. Kita-sangokan, 13-3, Nishitenma 5-chome, Kita-ku, Osaka-shi, Osaka 530-0047 Japan, hereby declare that:

1. I read and understand the Japanese and English languages.

2. I translated Japanese Patent Application No.205235/1997 (Heisei 9 nen) from Japanese into English.

3. The annexed document is, to the best of my knowledge and belief, an accurate translation of Japanese Patent Application No.205235/1997 (Heisei 9 nen).

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Osaka, Japan

Takayoshi Hirose

Takayoshi Hirose

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[Inventor]
[Domicile or Residence] c/o Nippon Meat Packers, Inc., Research and Development Center, 3, Midorigahara 3-chome, Tsukuba-shi, Ibaraki
[Name] Hiroshi Murakami
[Inventor]
[Domicile or Residence] c/o Nippon Meat Packers, Inc., Research and Development Center, 3, Midorigahara 3-chome, Tsukuba-shi, Ibaraki
[Name] Tatsuya Fujimura
[Inventor]
[Domicile or Residence] c/o Nippon Meat Packers, Inc., Research and Development Center, 3, Midorigahara 3-chome, Tsukuba-shi, Ibaraki
[Name] Yoichi Takahagi
[Inventor]
[Domicile or Residence] c/o Nippon Meat Packers, Inc., Research and Development Center, 3, Midorigahara 3-chome, Tsukuba-shi, Ibaraki
[Name] Koji Toyomura
[Inventor]
[Domicile or Residence] c/o Nippon Meat Packers, Inc., Research and Development Center, 3, Midorigahara 3-chome, Tsukuba-shi, Ibaraki
[Name] Tamotsu Shigehisa
[Applicant]
[Identification Number] 000229519
[Name] Nippon Meat Packers, Inc.
[Agent]
[Identification Number] 100085486

[Patent Attorney]

[Name] Takayoshi Hirose

[Attached Documents]

[Name of Document] Specification 1

[Name of Document] Drawing 1

[Name of Document] Abstract 1

[General Power Number] 9000995

【Name of the document】 Specification

【Name of the invention】 A transgenic mouse

【Claims】

【Claim 1】 A transgenic mouse carrying gene of a human complement inhibitor (DNA /CD55) and expressing the human complement inhibitor endothelial cells.

【Claim 2】 The transgenic mouse as claimed in claim 1, expressing the human complement inhibitor (DAF/CD55) in endothelial cells of all organs.

【Claim 3】 The transgenic mouse as claimed in claim 1 or 2, carrying promoter of the porcine complement inhibitor (pMCP) at an upstream locus of the human complement inhibitor (DAF/CD55) gene.

【Detailed explanation of the invention】

【0001】

【Technical field of the invention】

This invention provides a transgenic mouse. Particularly, the invention provides the transgenic mouse carrying the human complement-inhibitor (hDAF/CD55) gene.

【0002】

【Prior arts】

Recently, studies on animal-to-man organ transplantation (xenotransplantation) have been carried out mainly in European countries and the United States. Because of close relation to human beings, apes may be desirable donors, but the use of their organs may be infeasible because of the shortage of these animals and their high intelligence. However, domestic animals, particularly pigs, have advantages of their organ sizes and shapes similar to those of man, easy supply due to mass rearing and established basic technology. Consequently, organ transplantation from the pig to man has mainly been studied.

If a porcine organ is transplanted to man, it will immediately (within minutes)

and severely be rejected (hyperacute rejection), resulting in loss of its functions.

These phenomena are thought to be caused by a series of reactions: (1) Human blood contains endogenous antibodies against porcine cells (termed natural antibodies). If a porcine organ is transplanted to man, such antibodies recognize the porcine organ and form antigen-antibody complexes. (2) The antigen-antibody complexes activate complement in human serum and trigger the complement cascade reaction. The attachment of C1 to the antigen-antibody complexes triggers reactions of C4 and C2, resulting in formation of C3 convertase, which activates C3 and cleaves it to C3b and C3a. The attachment of C3b to the cell surface of the porcine organ results in formation of C5 convertase, which activates C5 and cleaves it to C5b and C5a. The attachment of C5b to the cell surface results in sequential attachments of C6, C7, C8 and C9. (3) In consequence of the complement cascade reaction, the membrane attack complex (MAC) is formed (termed the classical complement pathway). MAC attaches the transplanted organ and causes thrombosis. (4) The alternative complement pathway is known to cause also the same cascade reaction as described above after the C3 step and finally to form MAC.

Miyagawa, S. *et al.* (Transplantation, 46(6), 825-830, 1988) reported the following: (1) the complement cascade reaction triggered hyperacute rejection of xenografts via the classical and/or alternative pathway; (2) no hyperacute rejection occurred, if the recipients had previously been treated with CVF (cobra venom factor) to cause deprivation of C3. From such findings, it has long been desired to generate transgenic animals expressing membrane-bound DAF and/or MCP, especially those homologous to recipient species, which can inhibit the cascade reaction at the C3 step.

【0003】

It has been tried to generate transgenic pigs expressing a complement inhibitor hDAF (CD55) to decompose human C3 convertase in the porcine organs (Ariella M. Rosengard *et al.*, Transplantation, Vol. 59, No. 9, 1325-1333, 1995: G. Byrne *et al.*, Transplantation Proceedings, Vol. 28, No. 2, 759, 1996).

However, it has never been explained whether these transgenic pigs completely suppresses hyperacute rejection. Therefore, questions like the following should be answered: 1) Do these transgenic pigs express sufficient amounts of hDAF in target organs? 2) Is it necessary to co-express some other complement inhibitors? Thus, many problems are left unsolved to overcome the hyperacute rejection.

【0004】

【Subjects to be solved by the invention】

To solve these problems, it is urgent to generate small-sized laboratory animals that can be handled more easily than pigs and to examine these animals from various viewpoints. Particularly, in order to carry out studies in this field, it is valuable to generate the transgenic mice, of which tissues and organs express appropriate amount of hDAF.

Transgenic mice expressing hDAF have been generated (N. Cary *et al.*, Transplant. Proc. Vol. 25, No. 1, 400-401, 1993; D. Kagan *et al.*, Transplant. Proc. Vol.26, No. 3, 1242, 1994). The loci and amounts of hDAF expressed in these transgenic mice, however, varied from report to report. Strictly speaking, no transgenic mice expressing the human complement inhibitor (as membrane-bound molecules other than DAF, MCP and CD59 have been known) in the due organ (particularly, vascular endothelial cells) has ever been generated.

To solve the above problems, the present inventors studied to generate the transgenic mouse expressing hDAF in the due organs and tissues, particularly the vascular endothelial cells. The inventors succeeded in generating the transgenic mice fulfilling the purposes with the promoter of the porcine complement inhibitor (pMCP) previously invented by the inventors (see Japanese Patent Application No. 142961/1997), by introducing the transgene designed to express hDAF in the due organs and tissues, particularly in the vascular endothelial cells.

This invention was accomplished on the basis of such findings. The purpose of the invention was to provide the transgenic mouse useful in the medical and pharmacological fields.

【0005】

【Means to solve the subjects】

Summary of the invention to solve the above-described subjects is as follows:

① a transgenic mouse carrying gene of the human complement inhibitor (DNA/CD55) and expressing the human complement inhibitor in its endothelial cells;

② The transgenic mouse as described in ①, in which it expresses the human complement inhibitor (DAF/CD55) in the endothelial cells of all the organs thereof;

③ The transgenic mouse as described in ① or ②, in which it carry promoter of the porcine complement inhibitor (pMCP) at an upstream locus of the human complement inhibitor (DAF/CD55) gene.

【0006】

【The best mode for applying the invention】

As described above, the transgenic mouse of the present invention is carrying the human complement inhibitor (referred to as hDAF in the following) and expressing the inhibitor in the vascular endothelial cells.

The transgenic mouse of the invention can be generated by the following methods:

First, transgene is prepared by binding promoter with hDAFcDNA. A part of an appropriate vector (e.g., pGL-3 basic vector, pBluescript and the like) is clipped out with a restriction enzyme(s), and the ends of the digested vector are truncated.

Base sequence encoding hDAF is clipped out from hDAFcDNA (see Medof, M. E. *et al.*, Proc. Natl. Acad. Sci. USA., 84, 2007, 1987 for example) at an upstream locus of the initiation codon and at a downstream locus of the termination codon with a restriction enzyme(s), conventionally truncated and inserted into the above-described vector. An appropriate promoter gene is also inserted at an upstream locus of the hDAFcDNA-introduced locus.

Any promoter can be used, as far as it can induce expression of hDAF in the murine body. A promoter of endothelin is an example. The inventors found that a

promoter of porcine complement inhibitor (pMCP) worked more efficiently. The base sequence of the promoter of pMCP is defined as SEQ ID NO:1 (see Japanese Patent Application No. 142961/1997).

From the vector thus prepared (circular gene), transgene is prepared by digesting the region including the promoter and hDAF with an appropriate restriction enzyme(s).

Methods to carry out the above-described processes can conventionally be performed.

【0007】

A transgenic mouse can be generated conventionally by microinjecting the above-described transgenes into the murine fertilized eggs (those at the pronucleus phase), implanting the eggs in the oviducts or uteri of female mice (recipient mice) synchronized to the pseudopregnancy, and obtaining the youngs

To find whether the generated youngs are transgenic, below-described dot blotting, PCR and the like can be used.

The transgenic mice thus generated can be propagated by conventionally crossbreeding and obtaining the youngs.

As shown in the below-described examples, it was confirmed that the transgenic mice of this invention were carrying hDAF gene and expressing hDAF in the endothelial cells of all the organs.

【0008】

【Effects of the invention】

The present invention is useful in the medical and pharmacological fields, exerting the following effects:

(1) If such organs as the heart, liver and kidney of the transgenic mice of this invention are contacted with human blood or transplanted in primates, it can be confirmed that hDAF effectively prevents hyperacute rejection caused by xenotransplantation.

(2) This invention makes it feasible to study hyperacute rejection-related

problems hard to be solved only by expression of the complement inhibitors themselves. Namely, the invention may answer the questions whether it is necessary to introduce factors to maintain homeostasis of the vascular endothelial cells (*e.g.*, thrombomodulin, etc.).

(3) If the transgenic mice of this invention are mated with those expressing some other complement inhibitor (human MCP or human CD59), synergic effects of the inhibitors can be examined.

(4) If the cells from the organs of the transgenic mice of this invention (*e.g.*, cells from the liver, kidney and the like) are cultured, put in an appropriate device, and connected with human patients *ex vivo*, it will supplement or substitute the functions of the damaged organs of the patients.

【0009】

【Examples】

The present invention will specifically be explained in detail with actual examples, but the scope of the invention is not restricted to these samples.

Example 1

① Construction of transgene

The transgene comprising pMCP's promoter and hDAFcDNA is prepared as follows:

From pGL-3 basic vector (Promega), *luc* gene was clipped out at the *Nco*I and *Xba*I sites. Both the ends of the digested vector were truncated with T4 DNA polymerase. Next, hDAFcDNA containing the first intron was clipped out at an *Asc*I site of the upstream locus of initiation codon ATG and at an *Acc*I site of the downstream locus of termination codon TAG, truncated with the T4 DNA polymerase and inserted into the above-described truncated vector. An approximately 5.4-kb promoter region was clipped out at the *BstE*II and *Eco*RI sites (the sequence from the second to the 5,392nd bases of SEQ ID NO:1) from the porcine genomic phage library of pMCP (Japanese Patent Application No. 142961/1997), truncated with T4 DNA polymerase (the sequence from the second to

the 5,397th bases of SEQ ID NO:1), and then inserted into an *Sma*I site at an upstream locus of the above-described hDAFcDNA-inserted vector (see Fig. I).

As a comparative example, a transgene comprising hDAF promoter and hDAFcDNA was prepared as follows: hDAF promoter gene was prepared by clipping out an approximately 3.8-kb region corresponding to the promoter at the *Hind*III and *Asc*I sites, truncated and inserted to an *Sma*I site at an upstream locus of the hDAFcDNA-inserted vector (see Fig. 2).

A region containing the above-described promoter and hDAFcDNA was clipped out at the *Not*I and *Eco*47III sites from each circular vector, dissolved in phosphate-buffered saline (PBS) at 5 μg/ml and used as the transgene.

【0010】

② Generation of the transgenic mouse

The transgenes were introduced into murine fertilized eggs and the transgenic mice were generated as follows.

CBA or C3H male and C57BL/6 female mice were mated to obtain baby mice, of which female mice (donor mice) were used to supply fertilized eggs. The donor mice were mated with ICR male mice after inducing ovulation (by administration of PMSG and hCG). The fertilized eggs (at the prenucleus phase) were collected. The above-described transgene (5 μg/ml) was introduced by microinjection into the prenuclei until their swelling was confirmed. The transgene-injected prenucleus-phase eggs were implanted in the uteri of the recipient mice immediately after transduction or in their oviducts after additional incubation for 3 days, and then baby mice were obtained. The recipient mice were made pseudopregnancy by mating them with vasoligated male mice.

【0011】

③ Identification of the transgenic mouse

Genomic DNA was extracted from the tails of the youngs obtained from the recipient mice and subjected to identification and selection of the transgenic mice by the following two methods:

(1) The dot-blotting method: Genomic DNA (10 μg) from the youngs was placed on a piece of membrane and hybridized with gene comprising a part of biotin-labeled hDAFcDNA. The transgenic mice (Tg mice) were identified by detecting the introduced transgene by an alkaline phosphatase-dependent photon-generating reaction (Sumalight, Sumitomo Metal, Inc.).

(2) PCR method: PCR was carried out (condition; denaturation for 30 sec at 94℃ and annealing for 2 min and 30 sec at 68℃, 30 times) with genomic DNA from the youngs as a template, 5'-GGCTGCTGCTGCTGGTGCTGTTGT-3' of hDAFcDNA as a sense primer and 5'-TCCATAATGGTCACGTTCCCCTTG-3' as an antisense primer. The transgenic mammals were identified by detecting the introduced transgene.

【0012】

④ Propagation of the transgenic mouse

The mice confirmed to be transgenic were mated with ICR mice, and then baby mice carrying the transgene were generated (termed TgF1 mice).

【0013】

⑤ Confirmation of expression of the transgene (transcription of mRNA)

By the conventional RT-PCR method, mRNA from various organs of the TgF1 mice was examined for transcription of hDAFcDNA. For comparison, mRNA from those of the transgenic mice generated with transgene comprising hDAF promoter and hDAFcDNA and mRNA from those of normal mice (nontransgenic mice) were similarly examined for transcription of hDAFcDNA. The results are shown in Fig. 3. B, H, K, Li, Lu, S and T in Fig. 3 stand for the brain, heart, kidney, liver, lung, spleen and testis, respectively.

With the transgenic mouse generated by introducing the transgene comprising pMCP promoter gene and hDAFcDNA (see Fig. 1), strong signals indicating transcription of mRNA of hDAF were confirmed in all the organs examined (the brain, heart, kidney, liver, lung, spleen and testis) (see Fig. 3A).

With the transgenic mouse obtained by introducing the transgene comprising hDAF promoter gene and hDAFcDNA (Fig. 2), signals of mRNA of hDAF were

observed only in the testis and brain, whereas no or faint signal in other organs (see Fig. 3B).

With the nontransgenic mice, no transcription of mRNA of hDAF was observed in any organ (see Fig. 3C).

With a cell line of human lymphocyte (K562), transcription of mRNA of hDAF was confirmed (see the right end of Fig. 3C).

【0014】

⑥ Confirmation of expression of the transgene (expression of the protein)

Frozen sections of the TgF1 mice organs were prepared and treated with biotin-labeled anti-hDAF monoclonal antibodies and then peroxidase-labeled streptavidin. After reaction with a chromogenic substrate (diaminobenzidine; DAB), the sections were microscopically examined for the intensity and the locus of the expressed hDAF protein. The results are shown in Table 1.

With the transgenic mouse generated by introducing transgene comprising pMCP promoter and hDAFcDNA, it was confirmed that all the organs examined were intensively expressing hDAF. The organs expressing hDAF were artial and ventricular myocardia, and endothelia of medium, small and capillary blood vessels of the heart, glomerulus, uriniferous tubule, and endothelia of medium, small and capillary blood vessels of the kidney, hepatocytes, epithelia of bile ducts, and endothelia of medium, small and capillary blood vessels of the liver, alveolar wall, bronchioles epithelium, and endothelia of medium, small and capillary blood vessels of the lung, epithelia of intestinal mucosa, and endothelia of medium, small and capillary blood vessels of the intestines, exocrine glands, Langerhans islets, epithilia and endothelia of medium, small and capillary blood-vessels of the pancreas, white and red pulp, trabeculare lienis, and endothelia of medium, small and capillary blood vessels of the spleen, cerebral and cerebellar cortex and medulla, and endothelia of medium, small and capillary blood vessels of the brain, seminiferous epithelia, interstitial cells, sperms, and endothelia of medium, small and capillary blood vessels of the testis and peripheral nerves.

With the transgenic mouse generated by introducing transgene comprising hDAF promoter gene and hDAFcDNA, the expression of hDAF was confirmed only in the testis, but not in the endothelial cells of the testis.

【0015】

[Table 1]

Table 1

Organ		Promoter		Normal mouse
		pMCP	hDAF	
Heart	Artial myocardium	++	−	−
	Venticular myocardium	+	−	−
	Endothelia of medium, small and capillary vessels	++	−	−
Kidney	Glomerulus	++	−	−
	Uriniferous tubule	−	−	−
	Endothelia of medium, small and capillary vessels	++	−	−
Liver	Hepatocytes	±	−	−
	Epithelia of bile duct	++	−	−
	Endothelia of medium, small and capillary vessels	++	−	−
Lung	Alveolar walls	++	−	−
	Bronchioles epithelium	++	−	−
	Endothelia of medium, small and capillary vessels	++	−	−
Intestines	Epithelia of intestinal mucosa	+	−	−
	Endothelia of medium, small and capillary vessels	++	−	−
Pancreas	Exocrine glands	+	−	−
	Langerhans islet	+	−	−
	Epithelia of pancreatic ducts	+	−	−
	Endothelia of medium, small and capillary vessels	++	−	−
Spleen	White pulp	±	−	−
	Red pulp	±	−	−
	Trabeculare lienis	+	−	−
	Endothelia of medium, small and capillary vessels	++	−	−
Brain	Cerebral cortex	++	−	−
	Cerebral medulla	++	−	−
	Cerebellar cortex	+	−	−
	Cerebellar medulla	++	−	−
	Endothelia of medium, small and capillary vessels	++	−	−
Testis	Seminiferous epithelia	++	±	−
	Interstitial cells	+	±	−
	Sperms	++	++	−
	Endothelia of medium, small and capillary vessels	++	−	−
	Peripheral nerve	+++	−	−

【0016】

As described above, it was confirmed that the transgenic mouse generated with the transgene comprising pMCP promoter and hDAFcDNA (Fig. 1) expressed mRNA from hDAFcDNA (see Fig. 3A) and hDAF protein (see Table 1) in the endothelial cells of the various organs thereof.

【0017】

SEQUENCE TABLE

SEQ ID NO:1

Length of sequence: 5,418

Type of sequence: nucleic acid

Number of chains: double strand

Topology: linear

Kind of sequence: Genomic DNA

Direct origin: λ FIXII porcine genome phage library

Sequence

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GAATTCTGCG TACACGGGGC CCCGGTGGCT TTACATCATC GCTACAGCGA     50
CATGGGATCC GAGCCGTGTC TACAACCTAC ACAACAACGC CAGATCCTTA    100
ACCCAATGCA TGAGGACAGG GCTCAAACCT GCGGCCTCAT AGATGCTAGT    150
CAGATTCGTT TCTGCTGAGC CACAATGGGA ACTCCTAATT CTAGATCGAT    200
CTAGAATTAG GAGTTCCCAT TGTGGCTCAG CAGAAACGAA TCTGACTAGC    250
ATCTATGAGG CCGCAGTTTG AGCCCTGTCC TCATGCATTG GGTTAAGGAT    300
CTGGCGTTGT TGTGTAGGTT GTAGACACGG CTCGGATCCC ATGTCGCTGT    350
AGCGATGATG TAAAGCCACC GGGGCCCCGT GCTACGCAGA ATTCNTGCAG    400
CCCGGGGGAT CCACTAGTTC TAGCNAGAGA GTTGAAAATT TAAAGAACAT    450
TTCTCCCCTA ATCTCCCAAA ATATGGGCAA AGGACAGGTA CCCGTGGCAC    500
TGGAAAAATA CAGGCAAGCA ACCCATGAGT ACATGAAAAG ATGCTCCAGG    550
GTTCGGCCTA ATGGAAGCCT GAACAATGCC TATCACATCG TGGGTTTCTG    600
AAGAAGTAAC TTAAAGAAAC TAGAAATTAA ATGGCTTTCT TAGAATGAAA    650
ATTCTCTATC ACAAGGAAAA ATGTTGTATG TTGTTTTTCC CATAATGGAG    700
GTCAGTGGGC GCTATGATTA ACAAATATCT GATGCCTGTG ACTTTTTAAT    750
TGCAAGAAAT CTGTGNAGTT TTTTTATTAT CTATGGGAAA TATTGCATAT    800
ATTAATGATA TCACCTAACT TGTATTATTG AGCAATTCTG TCCACATCTG    850
GCCTTTCATC TTTCATCTAA AAAGCAGGGG CTGGACCAAC TGACCTTCAG    900
TGCCATTCTT ACTGCTAACA TTCTAATTTT GTTTTTATTG CCTTTTTGTA    950
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CAAAAGTGTG AGAGAAGTCA TTTTAAGTCT GTGACATTAA ATGTAATTTT 1000
CTGTCTCCAG CATTATAATA AGAATCAAAG ATTTAATCTA ATACACCGAT 1050
GGAATATTGT TTATAACGTA TTTACTGTTT CAAGCCTTCA AAACCAAGAG 1100
AAAACAAAAT GAGTACCTGT TCCTTCTGAG AAATGCCCTT CTTCCTGTTC 1150
AGAATCCCTG TGTATAACAG GAATGCTCTC GAGTTAACAG CCAAGTAAGA 1200
GGCCCATCGG CTGGCAGGTG CCCACCTAGC TAGGTGCAAG CAGAGGTGGC 1250
AGTGCTCCCA GGACCAACAG CAGAAACATG GCTTAACTAT CCTGTGTTTA 1300
GCAGTTCTCT TACGGGTTTT CACAACACCT AAAAAGCGCC CTGATGGGGT 1350
AAAGCCTCTG CCTTCATGCT GCTGCCCCGT CTCTGAAAAG CAGGACGTAA 1400
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TCACGGTCAA TACTCCGCCC TTGGGCTCAG ACACTAAGAG GATCTCCGGG 1750
TAAAGAGATA GACAGTAGCT CCATGCCTGA TTTAGGAAAA CTGTCCGTAC 1800
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TTCCTGAAGT CATTAAAATC AAAAGCTCTC AGAAACGTCC CAGCATTTGC 1900
TAAGTCCACG CTGGGGGAGG ATGGGCAGAG CCGTGTTCAG CGCGTTTGAC 1950
AGCAACACCC ACTTATTTCA TTYAGTATCC ATAGGCATAT ATCATGCACC 2000
TGGTATAGGC CTCTCTCTCA GCACTGGAGA TACAGCAAGA AAACGCTATT 2050
CCTGCCCCAT GGAGCTTGTW MARAAAAATA GANNNAAAAA CCCTTTANAA 2100
ANGGAAGCTR CCNGMTGGGN CMAAGTNAAA ATTAAGTAAA AAGAAAWCCG 2150
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AAATTTTGCC TGACTCGTGC CAAAGATTGA GCCAGGGCCC GGGTGTCCAG 4850

```
GCAGTCTGCA GTGCCCCAGT CCCCACCAGA GCCCTGAAGG GTGTCGGGCC   4900
CCACGAAACC GCTGCCCGGG CTCTAGGGTT TCTGTTTTCA GGTCGCTGCG   4950
CTTTATTCTC TAATTCAGCG TTCCCGAAAG AGACCATGAG GACCCGCCCA   5000
GTGTCCTTTA CACCTTCCCG TGTCGGGTGG CGACAGCTGT TTACGAAGAA   5050
GAGTGCACCA CCCTTTCCCG CAAGCCGCAG CGGTTAGTTC CGCAGAAGGA   5100
GGAGCCAGGG CGTCGGGCCG CAGCTGGGAG AGAGGCCCGG CAGCGGGCGC   5150
CGCGGAGCAG CAAGGGCGTC CCTCTCTCGG CCGGAGCCCC GCCCCGCCCC   5200
GCCCCCACGG CCCCGCCTTG CGGCCCGCCC ATTGGCTCCG CCGGGCCCTG   5250
GAGTCACTCC CTAGAGCCAC TTCCGCCCAG GGCGGGGCCC AGGCCACGCC   5300
CACTGGCCTG ACCGCGCGGG AGGCTCCCGG AGACCGTGGA TTCTTACTCC   5350
TGCTGTCGGA ACTCGAAGAG GTCTCCGCTA GGCTGGTGTC GGGTTACCTG   5400
CTCATCTTCC CGAAAATG                                      5418
```

【Brief description of the drawings】

【Figure 1】

Figure 1 illustrates the structure of a transgene comprising pMCP promoter and hDAFcDNA.

【Figure 2】

Figure 2 illustrates the structure of a transgene comprising hDAF promoter and hDAFcDNA used for comparison.

【Figure 3】

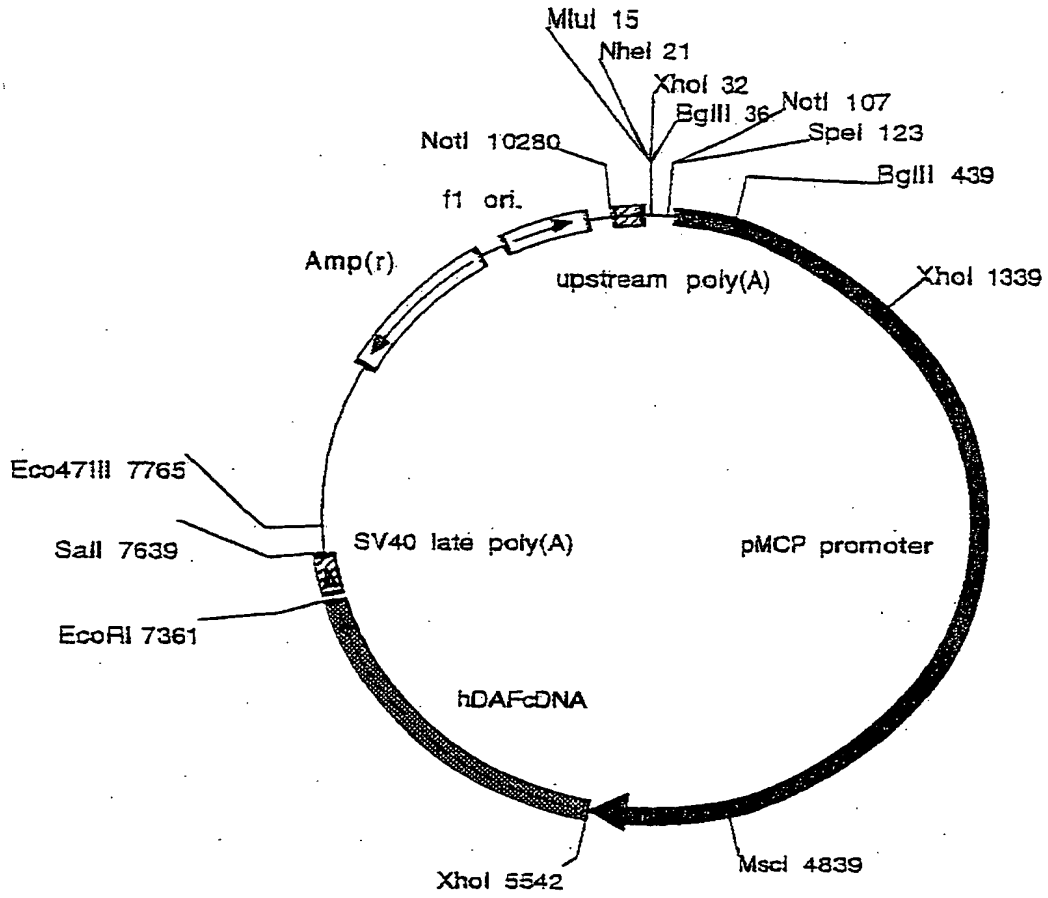
Figure 3 shows expression of mRNA of hDAF in various organs of a TgF1 mouse, a transgenic mouse generated for comparison and a normal mouse (nontransgenic mouse).

Expression of mRNA in various organs of the TgF1 mouse is shown in (A); that of the transgenic mouse for comparison (generated by introducing transgene comprising hDAF promoter and hDAFcDNA) (Fig. 2) is shown in (B); that of the nontransgenic mouse is shown in (C) and that of human lymphocyte (K562) at the right end of (C).

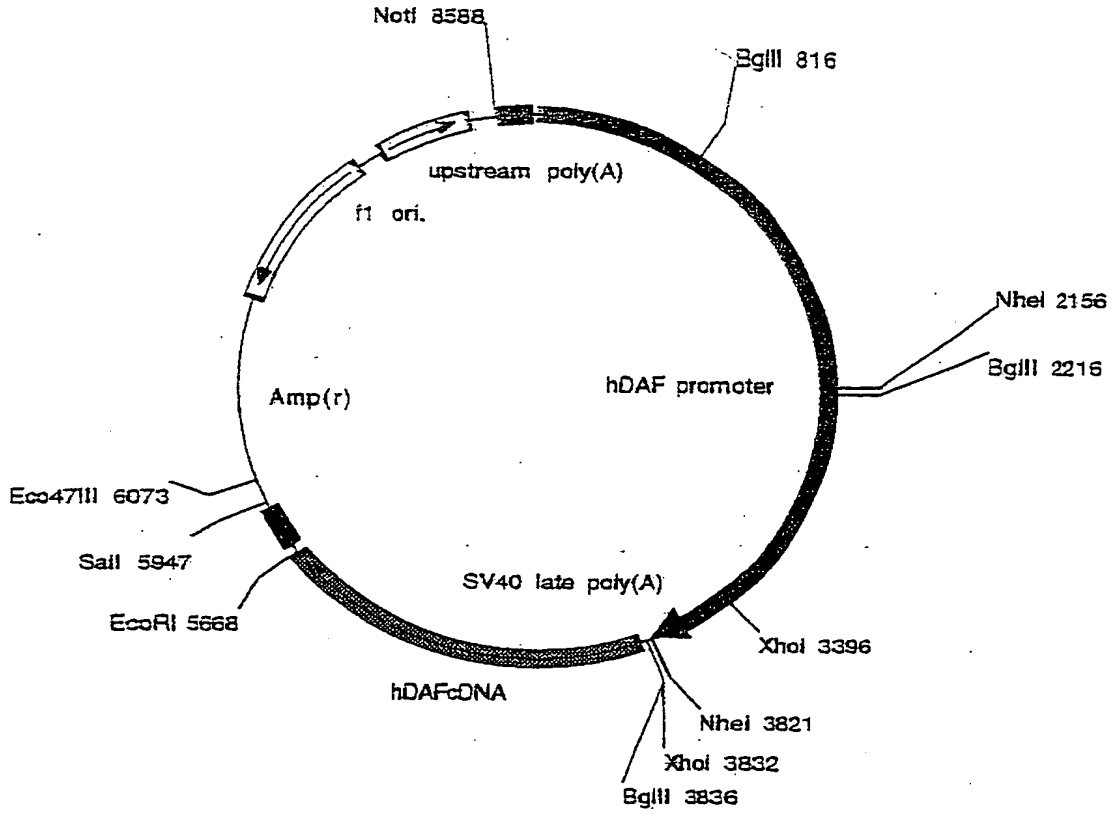
B, H, K, Li, Lu, S and T in each figure stand for the brain, heart, kidney, liver, lung, spleen and testis, respectively.

【Name of document】 Drawings

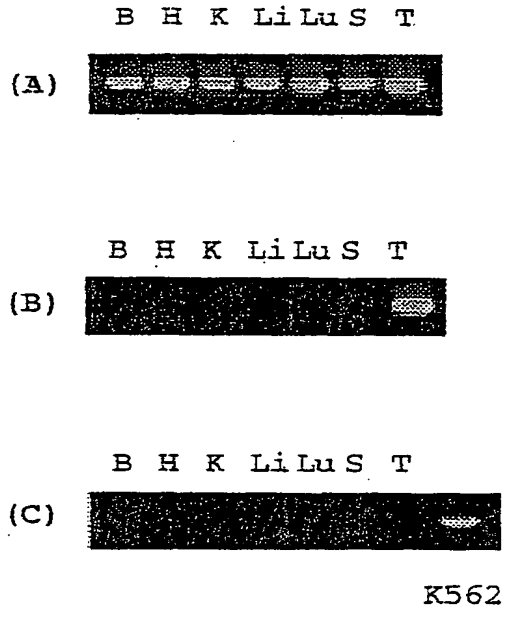
[Fig.1]



[Fig.2]


NotI 8588
BglII 816
upstream poly(A)
f1 ori.
NheI 2156
BglII 2216
hDAF promoter
Amp(r)
Eco47III 6073
SalI 5947
SV40 late poly(A)
EcoRI 5668
XhoI 3396
hDAFcDNA
NheI 3821
XhoI 3832
BglII 3836

[Fig.3]



【Name of document】 Abstract

【Abstract】

【Subject】 This invention provides a transgenic mouse.

【Means to solve the subject】 This invention provides a transgenic mouse carrying the gene of the human complement inhibitor (hDAF/CD55) and expressing the human complement inhibitor in the endothelial cells thereof. The transgenic mouse of this invention is useful as a laboratory animal in the medical and pharmacological fields.